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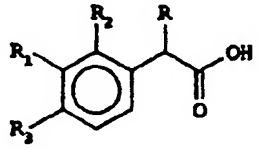
(54) Title: SOLUTIONS OF ARYL OR HETEROARYL SUBSTITUTED ALKANOIC ACIDS IN LIPOPHILIC SOLVENTS AND SOFT GELATIN CAPSULES CONTAINING SUCH SOLUTIONS

(57) Abstract

Methods and compositions are disclosed for preparing liquid mixtures of aryl or heteroaryl alkanoic acids suitable for encapsulation in soft gelatin capsules. The compositions comprise alkanoic acids of formulas (I), (Ia), (Ib) or pharmaceutically acceptable salts thereof, wherein R, R_1, R_2, R_3, and R_5 represent hydrogen or various organic substituents, and an effective solubilizing amount of at least one lipophilic solvent.



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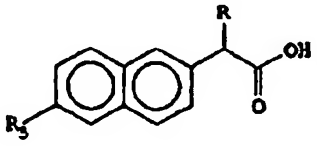

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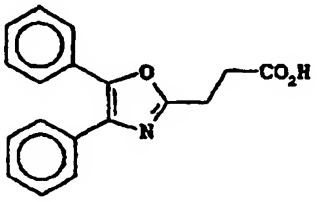

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SOLUTIONS OF ARYL OR HETEROARYL SUBSTITUTED ALKANOIC ACIDS IN LIPOPHILIC SOLVENTS AND SOFT GELATIN CAPSULES CONTAINING SUCH SOLUTIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to solutions containing therapeutically useful substituted alkanoic acids in combination with at least one lipophilic solvent for encapsulation in soft gelatin capsules (softgel capsules).

Description of the Related Art

Hydrophilic softgels are well known for the oral administration of pharmaceutical agents. Typically, softgel capsules consist of an outer shell of gelatin containing a plasticizer and an inner filling of hydrophilic liquid containing a dissolved hydrophobic pharmaceutical agent. The plasticizer is chosen so that the solubility in the fill liquid is as low as possible. If the plasticizer is soluble in the fill liquid, it can migrate out of the shell over time into the fill, leaving the shell brittle and subject to rupture.

With respect to pharmaceutical agents of relatively low solubility and/or relatively high dosage amount, softgel capsules can pose problems for the pharmaceutical formulator. For example, if a given pharmaceutical agent has a relatively low solubility, it may need a relatively large volume of solution in order to deliver a pharmaceutically acceptable unit dose. While theoretically possible to encapsulate such a large volume of solution in a softgel capsule, for example, the practical

limitations on the size of capsules suitable for conventional oral administration to human patients could well preclude pharmaceutical use of the resulting softgel.

Similarly, if a pharmaceutical agent requires a relatively high dose, a large volume of solution may again be a necessity for delivery of the require dosage. Softgel encapsulation of such a large solution volume may be impractical because the size of the needed softgel would likely exceed the maximum limit for conventional oral administration to human patients.

As one approach to handling the problems of encapsulating low solubility or high dose pharmaceutical agents, U.S. Patent No. 5,071,643 (Yu et. al.) discloses the use of polyethylene glycol based solutions for acidic, basic and amphoteric pharmaceutical agents. These polyethylene glycol based solutions contain either an hydroxide species or a hydrogen ion species that causes the appropriate pharmaceutical agent to partially ionize, i.e., the pharmaceutical agent is present in both the free form and the salt form. The partial ionization described in Yu et al. results in enhanced solubility for the acidic, basic or amphoteric pharmaceutical agent. This enhanced solubility, in turn, may permit the preparation of a solution of pharmaceutical agent that is highly concentrated enough to be encapsulated in a capsule acceptably sized for oral administration to human patients. The Yu et al. patent discloses that enhanced solubility solutions can be prepared using polyethylene glycol and contemplated equivalents of polyethylene

glycol, such as polyethylene glycol ethers or various alcohols and copolymers of polyethylene glycol.

Softgel encapsulation is sometimes the preferred delivery system for many pharmaceutical agents that are administered orally to human patients. Generally, to be suitable for softgel encapsulation, a pharmaceutical formulation should be in the form of a clear, stable solution. The present inventors have discovered that the enhanced solubility solutions disclosed by the Yu et al. patent are not as effective with various substituted alkanoic acid pharmaceutical agents.

Therapeutically useful 2- or 3-aryl or 2- or 3-heteroaryl substituted alkanoic acids function as anti-inflammatory and analgesic agents and may be administered orally. They are also essentially insoluble in water. An example of such a useful alkanoic acid suitable for use in the present invention is ketoprofen which is 2-(3-benzoylphenyl) propionic acid.

Ketoprofen is an anti-inflammatory, analgesic agent that is principally indicated for the acute and long-term management of rheumatoid arthritis and osteoarthritis. Additionally it is a nonsteroidal compound and poorly water soluble. Some gastrointestinal irritation is ordinarily associated with oral dosage forms of ketoprofen. The properties of ketoprofen render it a good candidate for formulation with the enhanced solubility solutions disclosed in the Yu et al. patent. In a number of experiments, the present inventors applied the Yu et al. enhanced solubility solutions in formulations of ketoprofen for softgel encapsulation.

In one formulation, polyethylene glycol 400 and potassium hydroxide were used to solubilize the ketoprofen, with the mole ratio of potassium hydroxide to ketoprofen being in the range of 0.4 to 1. It was surprisingly found that the resulting formulation was not sufficiently stable for softgel encapsulation due to the undesirable formation of ketoprofen esters.

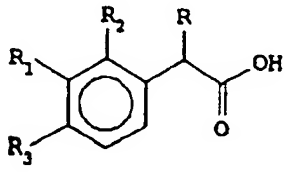
In an attempt to completely ionize the ketoprofen to prevent the formation of undesirable esters, the potassium hydroxide to ketoprofen mole ratio was adjusted to range from 1.1 to 1. With this second formulation, concerns arose that the ketoprofen salt thus formed and/or the high pH caused by the excess potassium hydroxide used could affect the physical stability of the softgel capsule when the formulation was encapsulated. Additionally, if an equilibrium amount of the ketoprofen free acid remained in the solution, it could form ketoprofen esters that could drive the reaction to form more ketoprofen free acid species, which could eventually result in a chemically unstable formulation.

The present inventors have discovered that non-hydroxyl containing solvents may be used to form pharmaceutically acceptable solutions of 2- or 3-aryl or 3-heteroaryl substituted alkanoic acids that are stable and suitable for softgel encapsulation.

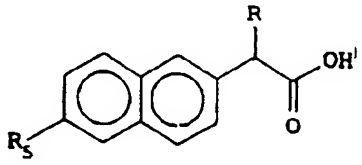
SUMMARY OF THE INVENTION

The present invention provides enhanced solubility pharmaceutically acceptable solutions of therapeutically useful substituted alkanoic acids, preferably 2- or 3-aryl or 2- or 3-heteroaryl alkanoic acids, that can be encapsulated in softgel capsules of a size suitable for subsequent oral administration to human patients, having improved chemical stability compared with polyethylene glycol water miscible formulations of the alkanoic acids.

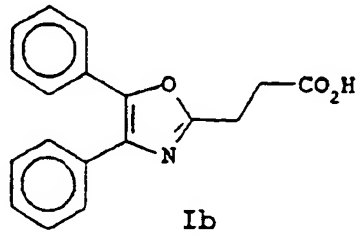
The therapeutically useful active agents, i.e., substituted alkanoic acids, preferred for use in the present invention have general formulas I, Ia or Ib:



I



Ia

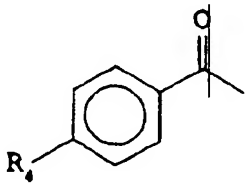


Ib

or pharmaceutically acceptable salts thereof, wherein

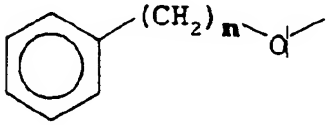
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 6 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

The enhanced solubility pharmaceutically acceptable solutions of therapeutically useful alkanoic acids can be encapsulated in softgel capsules of a size suitable for subsequent oral administration to human patients, which improves the physical stability of the softgel capsules used to encapsulate the pharmaceutical solutions compared with polyethylene glycol water miscible formulations of the alkanoic acids.

The present invention also provides enhanced solubility pharmaceutically acceptable solutions of alkanoic acids that unexpectedly can be encapsulated in a softgel capsule of a size smaller than what is required to encapsulate the same dose of the acid in polyethylene glycol water miscible formulations.

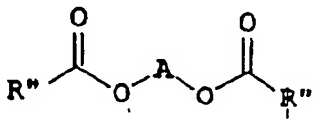
The enhanced solubility pharmaceutically acceptable solutions of 2- or 3-aryl or 3-heteroaryl alkanoic acids provided

by the present invention may reduce or eliminate the gastrointestinal irritation associated with oral dosage forms of these agents.

The lipophilic solvent and the hydroxyl containing softgel capsule plasticizers, such as glycerin, are immiscible, thereby improving both the chemical stability of the acid solution and improving the physical stability of the softgel capsule by greatly reducing the migration of capsule plasticizers into the encapsulated pharmaceutical formulation. Additionally, the use of the lipophilic solvent prevents the formation of esters which can decrease the chemical stability of the alkanoic acid solution.

Suitable lipophilic solvents are polyol esters of fatty acids. The polyol esters of fatty acids may be mono-, di-, tri-, etc, esters of the polyols. Thus, there may be free hydroxyl groups present in the polyol esters of fatty acids useful as lipophilic solvents of the invention.

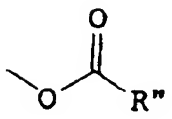
The lipophilic solvent preferred for use in the present invention is an alkylene glycol derivative of formula II:



II

wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or a group of the formula


; and

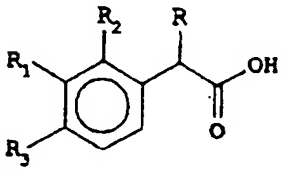
the R" groups are the same of different and represent C_1-C_{12} alkyl.

Further objects and embodiments of the present invention will be described in the following description of the preferred embodiments.

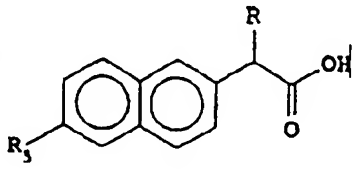
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is useful for providing pharmaceutically acceptable solutions of substituted alkanoic acids dissolved in at least one lipophilic solvent, which are chemically stable and suitable for softgel encapsulation.

The therapeutically useful active agents, i.e., substituted alkanoic acids, preferred for use in the present invention have general formulas I, Ia or Ib:



I



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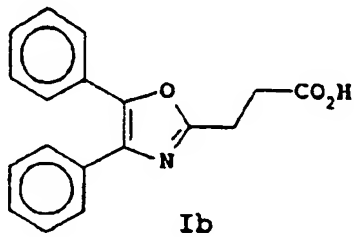


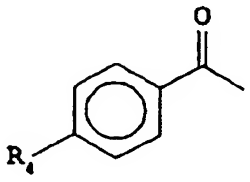
Ib

or pharmaceutically acceptable salts thereof,

wherein

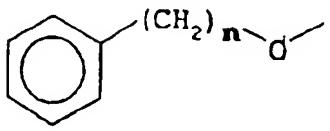
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

Suitable pharmaceutically acceptable, non-toxic salts include salts such as, for example, alkali metal, alkaline earth metal, ammonium and amine salts. Compounds of general formulas I, Ia, and Ib in which R represents an alkyl group can exist in optically active forms, including isomers and racemates thereof. Preferred alkanoic acids suitable for use in the present invention include ketoprofen (formula I where R is methyl, R_1 is benzoyl, and R_2 and R_3 are hydrogen, i.e., 2-(3-benzoylphenyl)propionic acid); ibuprofen (formula I where R is methyl, R_1 and R_2 are hydrogen, and R_3 is isobutyl, i.e., 2-(4-isobutylphenyl)propionic acid); naproxen (formula Ia where R is methyl and R_5 is methoxy, i.e., 2-(6-methoxy naphthyl)propionic acid); and oxaprozin, (formula Ib, i.e., 4,5-diphenyl-2-oxazolepropionic acid).

The enhanced solubility pharmaceutically acceptable solutions of therapeutically useful substituted alkanoic acids can be encapsulated in softgel capsules of a size suitable for

subsequent oral administration to human patients, which improves the physical stability of the softgel capsules used to encapsulate the pharmaceutical solutions compared with polyethylene glycol water miscible formulations of the alkanoic acids.

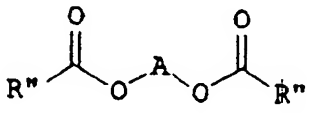
The present invention also provides enhanced solubility pharmaceutically acceptable solutions of ketoprofen that can be encapsulated in a softgel capsule of a size smaller than what is required to encapsulate the same dose of the acids in polyethylene glycol water miscible formulations.

The present invention provides pharmaceutically acceptable solutions containing from about 0.1 to 1000 mg, preferably about 5 to 200 mg, and most preferably about 10 to 100 mg, of an alkanoic acid dissolved in at least one lipophilic solvent, resulting in a clear solution suitable for softgel encapsulation. The lipophilic solvent and the hydroxyl containing softgel capsule plasticizers, such as glycerin, are immiscible, thereby improving both the chemical stability of the alkanoic acid solution and improving the physical stability of the softgel capsule by greatly reducing the migration of capsule plasticizers into the encapsulated pharmaceutical formulation. Additionally, the use of the lipophilic solvent prevents the formation of esters which can decrease the chemical stability of the alkanoic acid solution.

Suitable lipophilic solvents are polyol esters of fatty acids. The polyol esters of fatty acids may be mono-, di-, tri-, etc, esters of the polyols. Thus, there may be free hydroxyl

groups present in the polyol esters of fatty acids useful as lipophilic solvents of the invention.

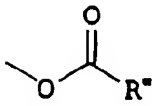
The lipophilic solvent preferred for use in the present invention is an alkylene glycol derivative of formula II:



II

wherein

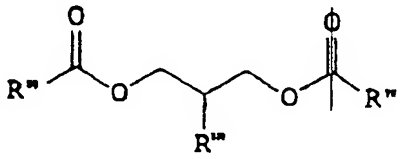
A represents C_1-C_4 alkylene optionally substituted with alkyl or



; and

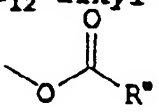
the R" groups are the same or different and represent C_1-C_{12} alkyl,

Suitable lipophilic solvents include those of formula III:



III

where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or



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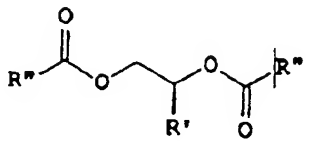
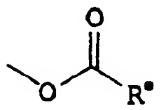
Suitable lipophilic solvents also include those of formula IV:



IV

where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

Other suitable lipophilic solvents are those of formula III where the R" groups are the same and represent C_1-C_4 alkyl and R''' is



Still other suitable lipophilic solvents are those of formula IV where the R" groups are the same or different and represent C_1-C_4 alkyl and R' is methyl.

Most preferred lipophilic solvents of formula III are those where R" is methyl. Most preferred lipophilic solvents of formula IV are those where the R" groups are the same or different and represent $CH_3(CH_2)_6$ or $CH_3(CH_2)_8$.

Particularly preferred solvents are selected from the group consisting of propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and mixtures thereof. Most preferably the solvents suitable for use in the present invention include

propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and mixtures thereof. Propylene glycol dicaprylate/dicaprate is available under the trade name Captex 200 from Karlshamn Lipid Specialties and 1,2,3-propanetriol triacetate is available under the trade name Triacetin from Eastman Chemicals.

The inventive solutions may also contain optional, additional ingredients to improve the dispersivity and dissolution of the substituted alkanoic acid. Suitable additional components include surfactants such as, for example, polyglyceryl esters of fatty acids, polyglycolyzed glycerides, propylene glycol esters, mono- and di-glycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol esters, polyoxyethylene acids, polyoxyethylene alcohols, and mixtures thereof. A preferred class of surfactants for use in combination with the lipophilic solvents is the polyoxyethylene sorbitan fatty acid esters. Suitable sorbitan esters are sold under the trade name Tween. A particularly useful Tween is polyoxyethylene (20) sorbitan mono-oleate (Tween 80).

The active substituted alkanoic acid pharmaceutical agent may be present in the solution in amounts ranging up to about 30% by weight of the solution. Preferred concentrations of the active agent are from about 5-20%, more preferably about 10-15%, by weight of the final solution. Combinations of lipophilic solvents may be used to obtain a desired final concentration.

For example, ketoprofen may be present in the solution in amounts ranging up to about 5% by weight of the solution when dissolved only in propylene glycol dicaprylate/dicaprate. Ketoprofen may be present in the solution in amounts ranging up to about 14% by weight of the solution when dissolved only in 1,2,3-propanetriol triacetate. When dissolved in a mixture of propylene glycol dicaprylate/dicaprate, 1,2,3-propanetriol triacetate and Tween, the ketoprofen pharmaceutical agent may be present in solution in amounts ranging up to about 22% by weight of solution.

In addition to the ketoprofen pharmaceutical agent and the lipophilic solvents, other adjuncts may optionally be present. Polyoxyethylene (20) sorbitan mono-oleate (Tween 80) may be included in the solution up to about 50% by weight of the solution.

Once the appropriate pharmaceutically acceptable solution of the substituted alkanoic acid is formulated, it can be encapsulated into conventional softgel capsules using any suitable encapsulation method, such as for example, the rotary die process.

All documents, e.g., patents and journal articles, cited above or below are hereby incorporated by reference in their entirety.

One skilled in the art will recognize that modifications may be made in the present invention without deviating from the spirit or scope of the invention. The invention is illustrated further by the following examples which are not to be construed

as limiting the invention or scope of the specific procedures described herein.

Example 1

Pharmaceutically acceptable solutions containing ketoprofen are prepared in the following manner. First, mix the following until homogeneous:

(1) about 92 mg of propylene glycol dicaprylate/dicaprate;

(2) about 92mg of 1,2,3-propanetriol acetate; and

(3) about 10 mg of polyoxyethylene (20) sorbitan mono-oleate.

Second, add about 25 mg of ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol acetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules, such as 4 oval softgel. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 2

Pharmaceutically acceptable solutions containing ketoprofen are prepared in the following manner. First, mix the following until homogeneous:

(1) about 112 mg of propylene glycol dicaprylate/dicaprate;

(2) about 72 mg of 1,2,3-propanetriol acetate; and

(3) about 14 mg of polyoxyethylene (20) sorbitan mono-oleate.

Second, add about 25 mg of ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol acetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules, such as 4 oval softgel. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 3

Pharmaceutically acceptable solutions containing up to about 22% ketoprofen by weight of solution are prepared in the following manner, which provides a self-emulsifying system. First, mix the following until homogeneous:

(1) propylene glycol dicaprylate/dicaprate in an amount ranging from about 40% to about 98% by weight;

(2) 1,2,3-propanetriol acetate in an amount ranging from about 1% to about 55% by weight; and

(3) polyoxyethylene (20) sorbitan mono-oleate in an amount ranging from about 1% to about 50% by weight.

Second, add ketoprofen to the homogeneous mixture of propylene glycol dicaprylate, 1,2,3-propanetriol triacetate and polyoxyethylene (20) sorbitan mono-oleate, and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 4

Pharmaceutically acceptable solutions containing up to about 14% ketoprofen by weight of solution are prepared in the following manner. First, mix the following until homogeneous:

(1) propylene glycol dicaprylate/dicaprate in an amount ranging from about 1% to about 50% by weight; and

(2) 1,2,3-propanetriol acetate in an amount ranging from about 50% to about 99% by weight.

Second, add ketoprofen to the homogeneous mixture of propylene glycol dicaprylate and 1,2,3-propanetriol acetate and mix again. While mixing in the ketoprofen, heat the mixture and maintain the temperature between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel

capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 5

Pharmaceutically acceptable solutions containing up to about 5% ketoprofen by weight of solution are prepared by mixing the ketoprofen with propylene glycol dicaprylate/dicaprate while heating the mixture. The temperature of the mixture should be maintained between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 6

Pharmaceutically acceptable solutions containing up to about 14% ketoprofen by weight of solution are prepared by mixing the ketoprofen with 1,2,3-propanetriol acetate while heating the mixture. The temperature of the mixture should be maintained between 110-125°F until the ketoprofen is dissolved. Once the ketoprofen is fully dissolved, the solution is then cooled and deaerated. After being cooled and deaerated, the ketoprofen solution can be encapsulated in suitable softgel capsules. The filled softgel capsules are thereafter dry finished to the appropriate hardness.

Example 7

The following formulations are prepared according to the invention using the procedure set forth above in Example 1.

Ingredient	A (mg)	B (mg)	C (mg)
Propylene glycol dicaprylate/dicaprate	92	184	276
1,2,3-Propanetriol triacetate	92	184	276
Polyoxyethylene (20) sorbitan mono-oleate	10	20	30
Ketoprofen	25	50	75
Final softgel size	4 oval	7.5 oval	12 oval

Example 8

The following comparative formulations are prepared essentially as in the procedure set forth above in Example 1 but do not include the lipophilic solvent according to the invention.

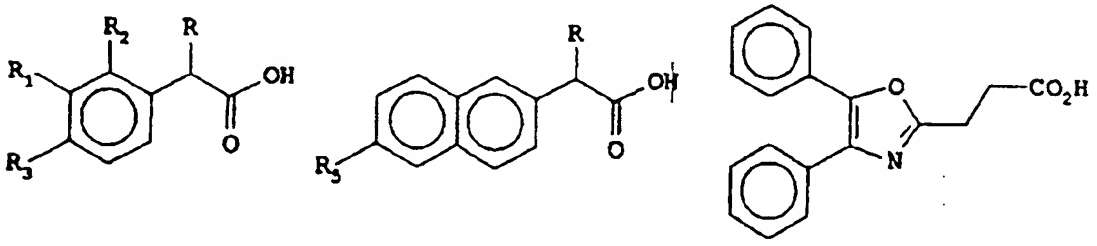
Ingredient	D (mg)	E (mg)	F (mg)
Water	5.46	10.92	16.38
Potassium hydroxide	6.06	12.12	18.18
Polyoxyethylene glycol 400	438.48	876.96	1315.44
Propylene glycol	25	50	75
Ketoprofen	25	50	75
Final softgel size	12 oval	20 oval	30 oval

Certain specific embodiments of the present invention have been discussed and disclosed in detail. Many other embodiments

that have not been disclosed or described are nevertheless the equivalent of and fall within the scope of the present invention and/or the following claims.

WE CLAIM:

1. A pharmaceutical composition comprising alkanoic acids selected from the group consisting of alkanoic acids of the formulas:

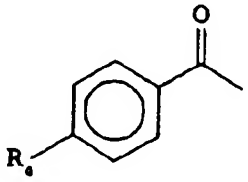


or pharmaceutically acceptable salts thereof,

wherein

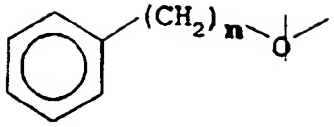
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



where n is 0, 1 or 2;

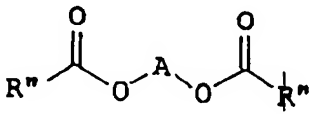
R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

R_5 is C_1-C_6 alkoxy.

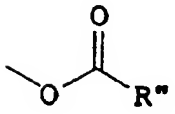
the 2-phenyl or naphthyl alkanoic acid being solubilized in a lipophilic solvent.

2. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



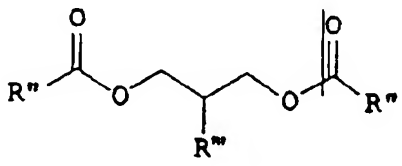
wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or

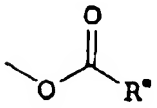
 ; and

the R" groups are the same of different and represent C_1-C_{12} alkyl.

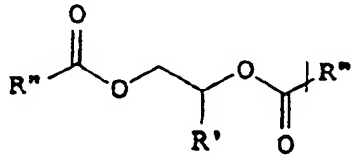
3. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or

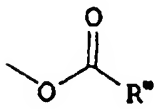


4. A pharmaceutical composition according to Claim 1 wherein the lipophilic solvent has the formula:



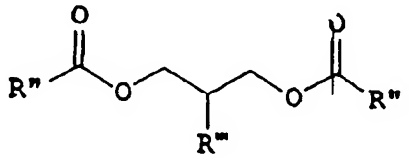
where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

5. A pharmaceutical composition according to Claim 3, where the R" groups are the same and represent C_1-C_4 alkyl and R''' is

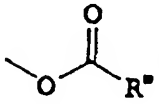


6. A pharmaceutical composition accoriding to Claim 4, where the R" groups are the same or different and represent C_1-C_4 alkyl and R' is methyl.

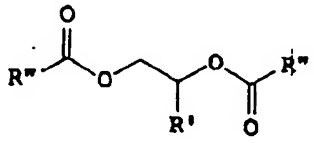
7. A pharmaceutical composition accoriding to Claim 1, wherein the lipophilic solvent comprises a mixture of a alkylene glycol derivative of the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R''' is hydrogen or

 and

a alkylene glycol derivative of the formula:



where the R" groups are the same or different and represent C_1-C_{12} alkyl and R' is C_1-C_6 alkyl.

8. A pharmaceutical composition of Claim 1 wherein at least one lipophilic solvent has no free hydroxyl groups.

9. A pharmaceutical composition comprising ketoprofen, naproxen, oxaprozin or ibuprofen solubilized up to 14% by weight in 1,2,3-propanetriol triacetate.

10. A pharmaceutical composition comprising ketoprofen, ibuprofen, oxaprozin or naproxen solubilized up to 5% by weight in propylene glycol dicaprylate/dicaprate.

11. The pharmaceutical composition of Claim 9, wherein the ketoprofen, naproxen, oxaprozin or ibuprofen is solubilized in a mixture of 1 to 50% by weight of propylene glycol dicaprylate/dicaprate and 50 to 99% by weight of 1,2,3-propanetriol triacetate.

12. A pharmaceutical composition comprising ketoprofen, oxaprozin, naproxen, oxaprozin or ibuprofen solubilized up to 22% by weight in a mixture of 40 to 98% by weight of propylene glycol dicaprylate/dicaprate, 1 to 55% by weight of 1,2,3-propanetriol triacetate, and 1 to 50% by weight of a surfactant.

13. A solution comprising from about 0.1 to about 30% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

14. A solution according to Claim 13, comprising from about 5 to about 20% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

15. A solution according to Claim 13, comprising from about 10 to about 15% by weight of ibuprofen, naproxen, oxaprozin or ketoprofen in a lipophilic solvent.

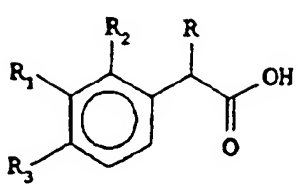
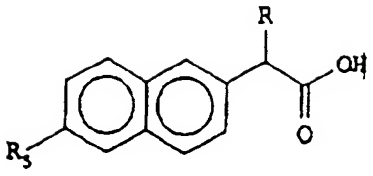
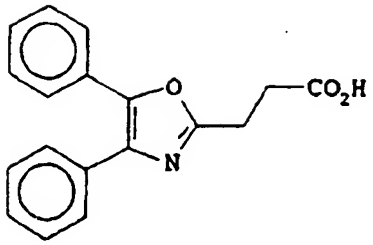
16. A soft gelatin capsule comprising a solution of ketoprofen, naproxen, or ibuprofen in a lipophilic solvent.

17. A soft gelatin capsule according to Claim 16, wherein the amount of ketoprofen, naproxen, oxaprozin or ibuprofen in the solution is from about 10 to 15% by weight of the solution.

18. A solution according to Claim 13, wherein the lipophilic solvent is suitable for encapsulation by a gelatin shell.

19. A pharmaceutical composition comprising an amount of ketoprofen, ibuprofen, oxaprozin or naproxen effective to produce analgesia in a patient, the ketoprofen, ibuprofen, oxaprozin or naproxen being present as a solution in a pharmaceutically acceptable lipophilic solvent.

20. A method for preparing a liquid mixture of a 2- or 3-aryl or 3-heteroaryl alkanoic acid suitable for encapsulation in a soft gelatin capsule comprising mixing a 2- or 3-aryl or 3-heteroaryl alkanoic acid of the formula:

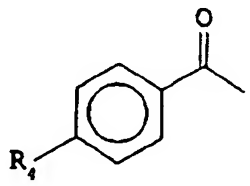




or pharmaceutically acceptable salts thereof,

wherein

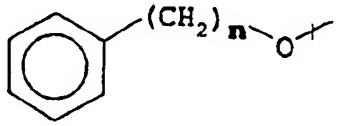
R represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms;

R_1 represents hydrogen, halogen, C_1-C_6 alkyl, phenylalkyl where the alkyl is C_1-C_6 alkyl, a benzoyl group of the formula:



where R_4 represents hydrogen, C_1-C_6 alkyl, or an alkylthio group having 1 to 4 carbon atoms; or

R_1 represents a group of the formula:



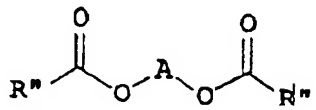
where n is 0, 1 or 2;

R_2 represents hydrogen, hydroxy or C_1-C_6 alkoxy;

R_3 represents hydrogen, C_1-C_6 alkyl or phenyl; and

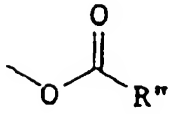
R_5 is C_1-C_6 alkoxy,

with an effective solubilizing amount of at least one lipophilic solvent of the formula:



wherein

A represents C_1-C_4 alkylene optionally substituted with alkyl or

 ; and

the R" groups are the same of different and represent C_1-C_{12} alkyl.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/19 A61K47/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A,5 059 626 (PARK MOO W ET AL) 22 October 1991 see column 1, line 59 - line 60; example 1; table II	1-7,9, 10,13-20 8,11,12
X Y	WO,A,92 08445 (AFFINITY BIOTECH INC) 29 May 1992 see claims 1-3	1-6,9, 10,13-20 7,8,11, 12
X Y	US,A,4 727 109 (SCHMIDT PETER C ET AL) 23 February 1988 see claims 1-8; examples 4,7,8	1-7,9, 13-20 8,10-12
Y	WO,A,92 10996 (MERRELL DOW PHARMA) 9 July 1992 see page 7, paragraph 1; claims 1-3	7,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 September 1995	27. 10. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Foerster, W

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 071 643 (YU MAN S ET AL) 10 December 1991 cited in the application see example IX; table 1 ---	1-20
A	WO,A,94 07488 (PFIZER ;AHMED IMRAN (US)) 14 April 1994 see the whole document -----	1-20

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		NO-A-	951350	06-06-95
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